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PATENT SPECIFICATION

1121307



NO DRAWINGS

1121307

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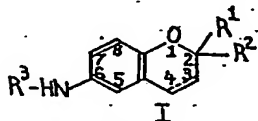
COMPLETE SPECIFICATION

New Chromans and Chromenes

We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1, a company incorporated in England, do hereby declare this invention which was communicated from Burroughs Wellcome & Co. (U.S.A.) Inc., a company incorporated in the State of New York, of 1, Scarsdale Road Tuckahoe 7, New York, United States of America, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to chroman and chromene derivatives, and the manufacture thereof.

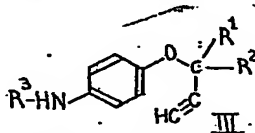
The present invention provides new compounds represented by the general formula (I)



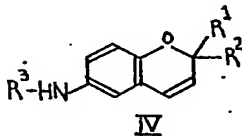
wherein R¹ and R² are the same or different and each is a lower alkyl group, R³ is a hydrogen atom or a lower alkanoyl group, and the broken line denotes that a double bond may be present in that position. The terms "lower alkyl" and "lower alkanoyl" are denoted to mean up to 5 carbon atoms.

These new compounds have pronounced anti-depressant, analgesic and anti-pyretic properties. Some of them possess activity against paratitic flat worms of the order of trematodes.

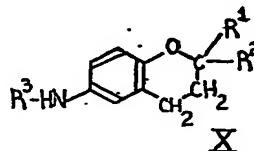
The compounds of formula (I) can conveniently be prepared by a thermal rearrangement or cyclization of the corresponding compounds of formula (III)



wherein R¹, R² and R³ are as defined in formula (I), into a compound of the formula (IV)

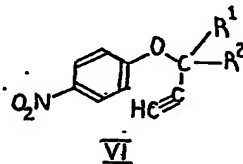


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which may, if desired, be reduced to a compound of formula (X) by catalytic hydrogenation.

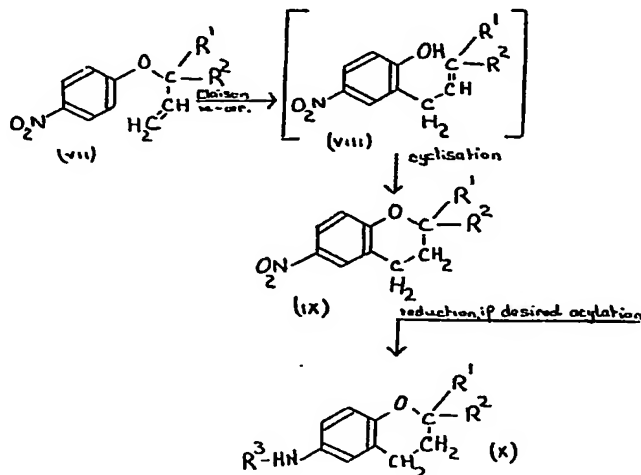
The compounds of formula (III) may conveniently be provided by the reduction of the corresponding compounds of formula (VI)



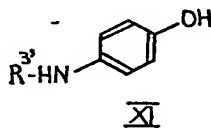
and, if desired, by subsequent acylation.

The cyclisation of a compound of formula (III) takes place at elevated temperatures, usually around 100 to 120° C. In the case of the lower members of the group, for instance 3 - (4 - acetamidophenoxy) - 3 - methyl - but - 1 - yne with a melting point of 85° C, the reaction can be brought about by distillation at 0.01 mmHg. (110 to 120° C). With the corresponding amine ($R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$), the conversion requires higher temperatures.

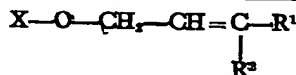
The chromans of formula (X) can also be prepared by a method, which is believed to be a Claisen (thermal) re-arrangement at elevated temperatures and cyclization of the corresponding compound of formula (VII). The reaction may be assumed to proceed through an intermediate compound of formula (VIII) to form a compound of formula (IX) which is then reduced and, if desired, acylated to produce a compound of formula (X).



Chromans of formula (X) can also be prepared by a method comprising the steps of reacting a compound of formula (XI).

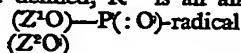


with a compound of formula (XII)



(XII)

and converting, if desired, the protected amino group into a free amino group; wherein R¹ and R² are as hereinbefore defined, R³ is an alkanoyl group, and X is either a



5 in which Z¹ and Z² are the same or different and each is a phenyl group or a phenyl group, optionally substituted in the ortho or para position with an electron withdrawing substituent, such as a nitro, halogeno, sulphonic acid or acetyl substituent, or X is a Z³-SO₂-radical, in which Z³ is a lower hydrocarbon having from 2 to 4 carbon atoms, or a phenyl group, tolyl group, or either of these aromatic groups appropriately substituted with an electron withdrawing radical. Within 10 the limitation of this definition the exact nature of Z¹, Z² or Z³ is relatively unimportant and irrelevant as these groups are eliminated in the reaction. In a particular aspect there is provided a method, which uses an appropriate 3 - disubstituted - allyl-*p* - toluene sulphonate or 3 - disubstituted - allyl diphenyl phosphate as a reagent.

15 It is advantageous to carry out the reaction in a solvent free medium or in the presence of non-polar solvents.

In one aspect therefore the present invention provides compounds of the formula (I). In another aspect there is provided a method, in which a corresponding compound of formula (III) is cyclised at elevated temperatures followed, if desired, by catalytic 20 hydrogenation to produce the compound of formula (I).

In a particular aspect a method is provided for the production of chromans of formula (X), in which the corresponding compounds of formula (VII) are converted into a compound of formula (IX) which is then reduced to the amine and, the latter, if desired, acylated. In a further particular aspect a method is provided for the production of chromans of formula (X), in which the corresponding compound of formula (XI) is reacted with a compound of formula (XII), and, if desired, the protected amino group is converted into a free amino group.

The compound of formula (I) and addition salts thereof with a pharmaceutically acceptable acid when R³ is a hydrogen atom, may be presented with an acceptable carrier in pharmaceutical compositions for human and veterinary use, made by any method comprising the admixture of the components. For oral administration, fine 30 powders or granules of the compound or salt thereof may contain diluents and dispersing and surface active agents, and may be presented in a draft in water or in a syrup; in capsules or cachets in the dry state or in a non-aqueous suspension, when a suspending agent may be included; in tablets when binders and lubricants may be included; or in a suspension in water or a syrup or an oil, or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included; the granules or the tablets may be coated. For parenteral administration, the compound or salt thereof may be presented in aqueous or non-aqueous injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render 40 the compound isotonic with the blood; or in aqueous suspensions when suspending agents and thickening agents may be included; extemporaneous injection solutions may be made from sterile pills; granules or tablets which may contain diluents, dispersing and surface active agents, binders and lubricants. The compound or salt thereof 45 may also be presented in suppositories or pessaries by incorporation in a suppository base.

In a further aspect therefore pharmaceutical preparations are provided for human and veterinary use, which contain a compound of the formula (I) or an acid addition salt thereof when R³ is a hydrogen atom, in an acceptable carrier, and the method of making such preparations by the admixture of the components.

The following examples illustrate the invention:—

EXAMPLE 1

3 - (4 - Nitrophenoxy) - 3 - methyl - but - 1 - yne (87% pure by acetylenic hydrogen titre) (16 g.) was dissolved in 95% ethanol (60 ml.) in a flask equipped with a mechanical stirrer, a condenser set for reflux, and a device for the addition of solids. Concentrated hydrochloric acid (4 ml.) and, immediately with rapid stirring, electrolytic iron powder (36 g.) were added. The solution spontaneously heated to reflux temperature. It was stirred for half an hour after the addition of iron was completed, and was treated with 50% w/v aqueous sodium hydroxide (8 ml.) followed by anhydrous potassium carbonate (20 g.).

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Steam distillation of the resulting solution was carried out in the usual way. The first, clear steam distillate (3 litres) presumably contained the product in a form solubilized with ethanol. The second distillate (3 litres) contained an oil which soon solidified. The third distillate (3 litres) was essentially clear. The aqueous distillates were extracted with diethyl ether and an excess of acetic anhydride was added to the combined ethereal solution. After evaporating the ether and acetic anhydride, first at atmospheric pressure and later in a water-pump vacuum, a white solid was obtained. This was sublimed at about 170° C and 0.01 mmHg, giving a product of a m.p. 126—126.8° C. This was recrystallised from 1 part ethanol and 5 parts water, and a product identified as 2,2 - dimethyl - 6 - acetamido - chrom - 3 - ene (10 g.) was obtained.

A sample had two peaks and a shoulder in the ultra-violet, and hence was the styrene-like chromene rather than the simple aryl ether.

- A) λ max 323, E (molar) 3.39×10^3
- B) λ max 270, E (molar) 4.15×10^3 (shoulder)
- C) λ max 240, E (molar) 3.33×10^4

EXAMPLE 2

A sample (5 g.) of the chromene, obtained in Example 1, was dissolved in methanol and was hydrogenated in a Parr hydrogenator. Platinized charcoal catalyst was used, according to a method described by Baltzly, R., *J. Am. Chem. Soc.* (1952), 74, 4586, at a pressure of about 2 atm. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the methanol evaporated by heating in a water-pump vacuum. A white solid (4 g.) of a m.p. 108—109° C was obtained, which gave on recrystallisation from benzene-hexane 2,2 - dimethyl - 6 - acetamido - chroman of m.p. 110—111.5° C.

EXAMPLE 3

3 - (4 - Nitrophenoxy) - 3 - methyl - but - 1 - ene (17.6 g.) was dissolved in glacial acetic acid (100 ml.), and concentrated sulphuric acid (15 ml.) was added with constant swirling over about 3 minutes. The solution spontaneously warmed to about 60° C and was cooled indirectly with tap-water. A white precipitate crystallised from the solution, which was allowed to stand for another 2½ hours.

The precipitate was filtered and washed first with a little cold acetic acid and then with water. A further crop of precipitate was obtained by diluting the filtrate with water (about 1 litre), cooling the solution and filtering off the precipitate, which was then washed with water.

Both crops were separately dissolved in diethyl ether, and the ethereal solutions were washed with a saturated aqueous solution of sodium carbonate, dried with anhydrous magnesium sulphate and evaporated almost to dryness. The above first crop provided white crystals (10 g.) and the original second crop tan platelets (6 g.). The products were again separately recrystallised from hexane (each about 250 ml.), while charcoal was used for decolourisation in the second case. The resulting crystals were combined to give 2,2 - dimethyl - 6 - nitro - chroman, (15 g.) of a m.p. 102—103° C.

EXAMPLE 4

A sample (10.4 g.) of 2,2 - dimethyl - 6 - nitro - chroman, obtained in Example 3, was dissolved in 95% ethanol (150 ml.). The solution rapidly absorbed the theoretical amount of hydrogen in a Parr hydrogenator, while Adam's platinum oxide was used as a catalyst. The solution was then filtered to remove the catalyst and the solvent was removed by evaporation on heating in a water-pump vacuum.

The residual oil was taken up in diethyl ether and extracted from ether with 0.5N aqueous hydrochloric acid. The extract was basified with sodium hydroxide and re-extracted with diethyl ether. Evaporation of the dried ether solution left an oil (8.8 g.) which solidified. Two recrystallisations gave an off-white solid, identified as 2,2 - dimethyl - 6 - amino - chroman (6.7 g.) of m.p. 73.7—74.3° C.

EXAMPLE 5

A sample (2.6 g.) of the amine obtained in Example 4 was treated with acetic anhydride (2.6 ml.) in anhydrous diethyl ether (60 ml.) at room temperature. After 10 minutes the ether was evaporated in a steam bath, and the residual oil was dissolved in benzene-hexane. The solution was stored at -14°C, and crystals (2.5 g.) of m.p. 111.3—113° C were separated. The crystals were recrystallised from ethanol-water, and

the product was identified as 2,2 - dimethyl - 6 - acetamido - chroman (1.7 g.) of m.p. 113.3—113.7° C.

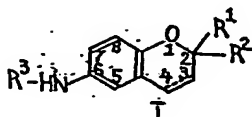
EXAMPLE 6

p-Hydroxyacetanilide (5.03 g., 0.034 mole) and 3,3 - dimethylallyldiphenyl phosphate (10.66 g., 0.034 mole) were mixed thoroughly so that the phenol was well distributed in the phosphate. The mixture was heated to 85° C for 15 h. in a sealed flask. The product, a dark-red oil, was dissolved in diethyl ether (75 ml.) and the insoluble solid was filtered off at a water pump. This was found to be 1.14 g. (24% return) of *p*-hydroxy-acetanilide, m.p. 167—169° C.

The ethereal filtrate was yellow in colour, and was extracted successively with dilute solutions of sodium bicarbonate, sodium hydroxide and hydrochloric acid before washing with water and drying over anhydrous magnesium sulphate. Evaporation of the ether yielded a viscous oil (10.9 g.), pale yellow in colour. This oil was then chromatographed on alumina (330 g.) with petrol (b.p. 40—60° C), and eluted successively with petrol, diethyl ether and 1:1 diethyl ether/ethyl acetate. These solvents did not produce any products from the column, except traces of terpenoid material derived from the phosphate. A very viscous oil (2.60 g.) was eluted with ethyl acetate, and this solidified overnight, m.p. 97—105° C. Recrystallisation twice from benzene-petrol gave a white, needle-like solid, m.p. 113—114° C, identified as 2,2-dimethyl - 6 - acetamido - chroman (yield 36%).

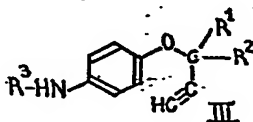
WHAT WE CLAIM IS:—

1. Compound of the formula (I)

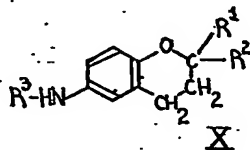
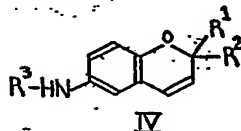


and addition salts thereof with a pharmaceutically acceptable acid when R² is a hydrogen atom, wherein R¹ and R² are the same or different and each is a lower alkyl group, R³ is a hydrogen atom or a lower alkanoyl group, as hereinbefore defined, and the broken line denotes that a double bond may be present in that position.

2. 2,2 - Dimethyl - 6 - acetamido - chrom - 3 - ene.
3. 2,2 - Dimethyl - 6 - acetamido - chroman.
4. 2,2 - Dimethyl - 6 - amino - chroman.
5. A method for the preparation of a compound of formula (I), in which a corresponding compound of formula (III)

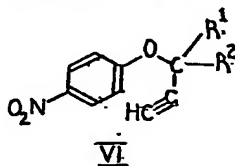


wherein R¹, R² and R³ are as defined in formula (I), is subjected to thermal rearrangement to produce a compound of formula (IV)



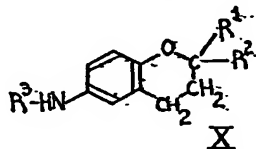
which may, if desired, be reduced, to a compound of formula (X) by catalytic hydrogenation.

6. A method according to claim 5, in which a compound of formula (III) is provided by reduction of a corresponding compound of formula (VI)

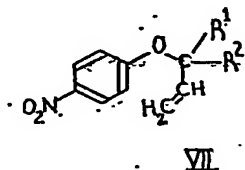


and, if desired, by subsequent acylation.

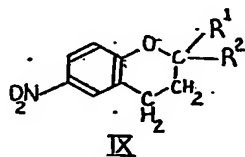
7. A method for the preparation of a compound of formula (X)



wherein R¹, R² and R³ are as defined in claim 1, in which a corresponding compound of formula (VIII)

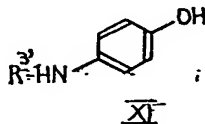


converted into a compound of formula (IX) by Claisen re-arrangement at elevated temperatures, and cyclisation

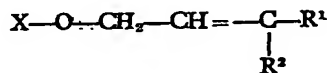


which is then reduced to the amine, and the latter, if desired, acylated.

8. A method for the preparation of a compound of formula (X), wherein R¹, R² and R³ are as defined in claim 1, in which a corresponding compound of formula (XI)

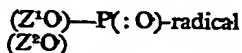


is reacted with a compound of formula (XII),



(XII)

and, if desired, the protected amino group is converted into a free amino group, wherein R^{3'} is an alkanoyl group, as hereinbefore defined, and X is either a



5 in which Z^1 and Z^2 are the same or different and each is a phenyl group, or a phenyl group optionally substituted in the ortho or para position with an electron withdrawing substituent, or X is a $Z^3\text{-SO}_2\text{-radical}$, in which Z^3 is a lower hydrocarbon having from 1 to 4 carbon atoms, or a phenyl group, tolyl group, or either of these aromatic groups appropriately substituted with an electron withdrawing radical. 5

9. A method according to claims 5 and 6, substantially as described with reference to Examples 1 and 2.

10 10. A method according to claim 7, substantially as described with reference to Examples 3, 4 and 5. 10

11. A method according to claim 8, substantially as described with reference to Example 6.

R. F. HASLAM,
Chartered Patent Agents,
Agent for the Applicants.

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